An Algorithm Determining Delay Times in a Mark Graph for Smooth Signal Flowing

Kanji Hioka[1] hioka@ib.sci.yamaguchi-u.ac.jp
Yoshimasa Miwa[1] miwa@ib.sci.yamaguchi-u.ac.jp
Chen Li[2] chenli@ims.u-tokyo.ac.jp
Qi-Wei Ge[3] gqw@yamaguchi-u.ac.jp
Hiroshi Matsuno[1] matsuno@sci.yamaguchi-u.ac.jp
Satoru Miyano[2] miyano@ims.u-tokyo.ac.jp

[1] Graduate School of Science and Engineering, Yamaguchi University, 1677-1 Yoshida, Yamaguchi 753-8512, Japan
[2] Human Genome Center, Institute of Medical Science, University of Tokyo, 4-6-1 Shirokanedai, Minato-ku, Tokyo 108-8639, Japan
[3] Faculty of Education, Yamaguchi University, 1677-1 Yoshida, Yamaguchi 753-8513, Japan

Abstract

This paper introduce an algorithm, which was proposed by Li et al.[1], that determines the firing frequencies of transitions in a Petri net model, and we indicate an issue of this method. Then we propose an algorithm that we solves this issue. The availability of the proposed method is confirmed by observing the movements of tokens through the simulation of the Fas signaling pathway as an example.

Keywords: Petri net, signaling pathway, mark graph, delay time

1 Introduction

Signaling pathways are the information cascades that propagate a signal from the cell membrane to the cell nucleus, which is triggered by the attachment of ligands to the receptor. Signal propagations are performed by sequential state changes of substances by biochemical reactions such as phosphorylation and complex formation. It can be naturally considered that any of these substances should not be accumulated during the propagation of a signal. Li et al.[1] proposed an algorithm that determines the firing frequencies of transitions in a Petri net model of a signaling pathway based on the structure of the Petri net model. With this methods, we can obtain smooth signal flows which are illustrated by token movements in the Petri net model. However, with this method, all firing frequencies are determined uniquely, once the firing frequency of one transition has been determined. Hence, despite the existence of various reaction speeds in a signaling pathway, Li's method can not reflect this variety of reactions speeds. In this paper, we propose an algorithm that produces conditions with which smooth token flows in a given mark graph can be obtained. A mark graph is a restricted Petri net model, which allows us to make a discussion in a simplified manner.

2 Definition

[Definition 1] Let *TPN* be a timed Petri net. A *TPN* is called *retention free Petri net* if, for a place p in the *TPN*, the following condition is satisfied; $\sum_{t_i \in {}^\circ p} \beta(t_i, p) \cdot f_i = \sum_{t_j \in p^\circ} \alpha(p, t_j) \cdot f_j$, where f_i is the number of firings of a transition t_i per unit time and is called the firing frequency of t_i. ${}^\circ p$ and ${}^\circ p$ are sets of input transitions and output transitions of place p, respectively.

[Definition 2] A *mark graph* is a Petri net such that any place of the Petri net has exactly one input arc and one output arc. A transition without no input arc is called *source transition* and is denoted by $T_{sour} = \{t_1^{sour}, t_2^{sour}, \cdots, t_m^{sour}\}(m \geq 1)$ for a given Petri net. A transition where at least two input arcs are attached is called *synchronous transition* and is denoted by $T_{sync} = \{t_1^{sync}, t_2^{sync}, \cdots, t_n^{sync}\}(n \geq 1)$ for a given Petri net. A path $\mathcal{P} = t_1 t_2 \cdots t_k (k \geq 2)$ in a Petri net is called *synchronization-free path* (**SFP**) if both of $t_1, t_k \in T_{sour} \cup T_{sync}$ and $t_2, \cdots, t_{k-1} \in T - (T_{sour} \cup T_{sync})$ are satisfied. □

3 An Algorithm to Obtain Retention-Free Mark Graph

In order for tokens not to stay at any place p in a given mark graph, the amount of incoming tokens should be smaller than that of outgoing tokens for place p. In the case of a mark graph in Fig.1(a), the condition for place p_k at which no token is stayed is expressed as follows; $f_1 \cdot \frac{\beta_1 \cdot \beta_2 \cdots \beta_{k-1}}{\alpha_2 \cdot \alpha_3 \cdots \alpha_k} \cdot \beta_k \leq f_{k+1} \cdot \alpha_{k+1}$, and the firing frequency of t_{k+1} should be $f_1 \cdot \frac{\beta_1 \cdot \beta_2 \cdots \beta_{k-1} \cdot \beta_k}{\alpha_2 \cdot \alpha_3 \cdots \alpha_k \cdot \alpha_{k+1}}$ in order for tokens not to stay at place p_k. For the paths of **SFP** in Fig.1(b) that synchronize at transition t_a^{sync} $(a \geq 1)$, in order for tokens not to stay in each place p of these paths, the following two conditions should be satisfied; (1) the above condition for no-token-staying should hold for place p and (2) the firing frequency of t_a^{sync} should be determined so that tokens from all the incoming places of t_a^{sync} in **SFP** are consumed at the same time. The following formula fulfills the requirement of the above condition (2); $f_1 \cdot \frac{\beta_1 \cdot \beta_2 \cdot \beta_3 \cdots \beta_l}{\alpha_2 \cdot \alpha_3 \cdots \alpha_l \cdot \alpha_{l+1}} = f_{l+1} \cdot \frac{\beta_{l+1} \cdot \beta_{l+2} \cdot \beta_{l+3} \cdots \beta_m}{\alpha_{l+2} \cdot \alpha_{l+3} \cdots \alpha_m \cdot \alpha_{m+1}} = \cdots = f_{m+1} \cdot \frac{\beta_{m+1} \cdot \beta_{m+2} \cdot \beta_{m+3} \cdots \beta_n}{\alpha_{m+2} \cdot \alpha_{m+3} \cdots \alpha_n \cdot \alpha_{n+1}}$.

Fig.3 shows an algorithm that produces a retention-free mark graph MG when the underling mark graph has synchronous transitions. If a mark graph does not have a synchronous transition, it is sufficient to derive only the conditions for no-token-staying.

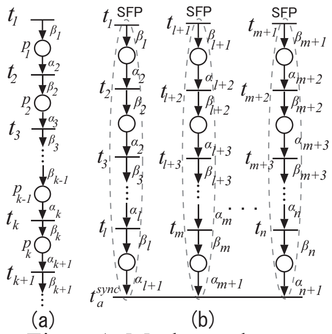

Figure1: Mark graph

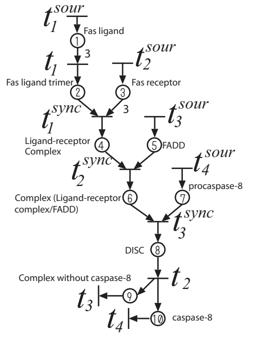

Figure2: A part of Fas signaling pathway

4 Example

We demonstrate the proposed method using the signaling pathway induced by Fas that is given in [1]. Fig.2 illustrates the part of this pathway that can be represented by mark graph. Our algorithm produces the set of following formulas. $f_1^{sour} \leq f_1 \cdot 3$, $\frac{f_1^{sour}}{3} \leq f_1^{sync}$, $f_2^{sour} \leq f_1^{sync} \cdot 3$, $\frac{f_1^{sour}}{3} = \frac{f_2^{sour}}{3}$, $\frac{f_1^{sour}}{3} \leq f_2^{sync}$, $f_3^{sour} \leq f_2^{sync}$, $\frac{f_1^{sour}}{3} = f_3^{sour}$, $\frac{f_1^{sour}}{3} \leq t_2^{sync}$, $f_4^{sour} \leq f_2^{sync}$, $\frac{f_1^{sour}}{3} = f_4^{sour}$. Furthermore, the following formulas are obtained based on the condition that incoming tokens are larger than outgoing tokens for place p in the downstream of transition t_2^{sync}; $f_2^{sync} \leq f_2$, $f_2 \leq f_3$, $f_2 \leq f_4$. From these formulas, we can obtain the firing frequencies at transitions of Fig.2 as follows; $f_1^{sour} = \frac{1}{2}, f_2^{sour} = \frac{1}{2}, f_3^{sour} = \frac{1}{6}, f_4^{sour} = \frac{1}{6}, f_1^{sync} = \frac{1}{3}, f_2^{sync} = \frac{1}{2}, f_3^{sync} = \frac{1}{3}, f_1 = \frac{1}{5}, f_2 = \frac{1}{2}, f_3 = \frac{1}{2}, f_4 = 1$. We conducted simulations of the signaling pathway of Fig.2 on Cell Illustrator [2] and smooth token flows were observed in the simulation.

SFP-SEARCH(MG)
1° $LT_{sync} \leftarrow t_1^{sync} \cdot t_2^{sync} \cdots$;
(t_j^{sync} is not ancestor on $t_i^{sync} (i < j)$)
2° $k = 1$;
3° Take out a top element of LT_{sync}, $LT_{sync} \leftarrow LT_{sync} - t$, $sfp \leftarrow t$;
4° $SFP_k = \phi$;
5° **for each** $p \in^{\bullet} t$;
6° $p' \leftarrow p$;
7° **repeat** ;
8° $t' \in^{\bullet} p' (|^{\bullet} p'| = 1)$;
9° **do if** $t' \in T^{sour} \cup T^{sync}$ **then**;
10° $SFP_k \leftarrow SFP_k \cup \{sfp\}$;
11° **break** ;
12° **else** $(|^{\bullet} t'| = 1)$;
13° $sfp \leftarrow t' \cdot sfp$;
14° $p' \in^{\bullet} t'$;
15° eq1(sfp);
16° eq2(SFP_k) ;
17° k++ ;
18° **if** $LT_{sync} = \phi$ **then** *stop*, **else** go to 3°;

Figure 3: An algorithm

5 Conclusion

Delay times of a given mark graph model of a signaling pathway can be obtained using the formulas produced from the algorithm proposed in this paper. By applying these delay times to the given mark graph model, we could obtain token movements that flow towards the bottom of the mark graph without staying at any places. However, a mark graph can only represent a limited part of signaling pathway. Hence, our next task is to enhance the proposed method to be applicable to more general Petri net models of signaling pathways.

References

[1] C. Li *et al.*, Modeling and simulation of signal transductions in an apoptosis pathway by using timed Petri nets, *Journal of Biosciences*, 32(1), 113–127, 2007.

[2] `http://www.cellillustrator.com/`